PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2006/040481	12.10.2006	12.10.2005

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/568 A61K9/06 A61K47/10 A61K47/14 A61K47/32 A61P15/00

Applicant
UNIMED PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Giró,Annalisa Telephone No. +49 89 2399-2763

Form (PCT/ISA/237) (Cover Sheet) (April 2005)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1-35 (i.a.)

because:

☒ the said international application, or the said claims Nos. 1-35 (i.a.) relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-44
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-44
Industrial applicability (IA)	Yes:	Claims	36-44
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1 to 35 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 02/17926 A (UNIMED PHARMACEUTICALS INC [US]; LAB BESINS ISCOVESCO [US]) 7 March 2002;
D2: WO 2004/037173 A (UNIMED PHARMACEUTICALS INC [US]) 6 May 2004;
D3: US 2005/113353 A1 (DUDLEY ROBERT E [US] ET AL) 26 May 2005;
D4: US 2005/020552 A1 (ASCHKENASY CHAIM [IL] ET AL) 27 January 2005;
D5: US 2004/072810 A1 (MASINI-ETEVE VALERIE [FR] ET AL) 15 April 2004.

Unless otherwise indicated, reference is made to the relevant passages emphasized in the International Search Report.

1. Clarity (Article 6 PCT).

1.1 Claims 1 (part "wherein after applying ..."), 17 to 21, 28 (part "wherein after applying ..."), 33, 36 (part "in amounts such that ...") to 38, 40 (part "in amounts such that ..."), 41, 43 (part "in amounts such that ...") do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims or part of the claims attempt to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

In this context, the following examination for said claims have been based on what the examiner considered to be the technical features referring to said claims or part of the claims, i.e., prima facie:
- for claims 1 and 17 to 21: a method of treating hypogonadism in a male subject comprising the steps a. and b. as claimed in claim 1;
- for claims 28 and 33: a method of treating hypogonadism in a male subject comprising the steps a. and b. as claimed in claim 28;
- for claims 36 to 38: a hydroalcoholic gel comprising a., b., c., d., e. as claimed in claim 36,
- for claim 40: a hydroalcoholic gel comprising a., b., c., d., e. as claimed in claim 40,
- for claim 43: a hydroalcoholic gel comprising a., b., c., d., e. as claimed in claim 43.

1.2 The term "Carbomer 980" used in claims 11 and 12 and appearing to be a registered trade mark has no precise meaning as it is not internationally accepted as a standard descriptive term, thereby rendering the definition of the subject-matter of these claims unclear under Article 6 PCT.

1.3 The term "carbomer" used in claims 25 to 28 is unclear because it appears to have different meanings in the art. In fact, in organic chemistry it can refer to a class of expanded molecules or it can be the tradename for synthetic polymers of acrylic acid. Therefore, claims 25 to 28 lack clarity under Article 6 PCT because it is not unambiguously clear which compounds fall within the scope of said claims.
In this context, the following examination for said claims have been based on what the examiner considered to be meant by that term, i.e., in the light of the description, synthetic polymers of acrylic acid.

1.4 The term "about" used to define ranges in claims 1 to 9, 14, 15, 22, 25 to 28, 30 and 32 is unclear because it leaves the reader in doubt as to the extreme values to consider included or not into said ranges, thereby rendering the definition of the subject-matter of said claims unclear under Article 6 PCT.
The attention of the Applicant is drawn to the fact that this unclarity might be relevant while establishing the novelty of said claims (see point 2.1)

2. Novelty (Article 33(2) PCT).
The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of independent claims 1, 28, 36, 40 and 43 is not new over documents

D1 to D4 in the sense of Article 33(2) PCT.

2.1 Document D1 discloses a method for treating hypogonadism in a male subject comprising the steps of:

a. providing a hydroalcoholic gel compositions comprising:

i. testosterone (1% w/w);
ii. isopropyl myristate (0.705 % w/w);
iii. ethanol (67% w/w);
iv. a thickening agent (Carbopol 980, a polymer of acrylic acid) in an amount (0.90% w/w) to give the composition a viscosity of more that 9000 cps;
v. 0.1N NaOH (4.72% w/w);
vi. water;

b. administering a therapeutically effective dose of the composition to an area of skin of the subject (see D1, Example 2)

The amount of 1% w/w of testosterone can be considered as included into the range of "about 1.15% to about 1.8% (w/w) of testosterone", as defined in independent claim 1 of the present application (see also clarity objections under point 1.4).

The same applies to the amount of 4.72% of 0.1 N NaOH, which is regarded as falling within the range of "about 6.5% to about 7.5% (w/w)", as claimed in present independent claim 28.

Therefore, the subject-matter of independent claims 1, 28, 36, 40 and 43 is regarded as not novel under Article 33(1) PCT over D1.

2.2 Also D2 to D4 disclose a method for treating hypogonadism in a male subject comprising the steps of:

a. providing a hydroalcoholic gel compositions comprising:

i. testosterone (D2, D3, D4: 1% w/w);
ii. isopropyl myristate (D2: 0.5 % w/w, D3, D4: 0.7 % w/w);
iii. ethanol (D2, D3: 67% w/w, D4: 69% w/w);
iv. a thickening agent (D2, D3: Carbopol 980, a polymer of acrylic acid in an amount (0.90% w/w) to give the composition a viscosity of more that 9000 cps; D4: Carbopol 940, no amount specified);
v. 0.1N NaOH (D2, D3: 4.72% w/w, D4: only in general, see par. [0122]);
vi. water;

b. administering a therapeutically effective dose of the composition to an area of skin of the subject (see D2, Table 4 and D3, Example 2)

As mentioned under point 2.1, the amount of 1% w/w of testosterone can be

considered as included into the range of "about 1.15% to about 1.8% (w/w) of testosterone", as defined in present independent claim 1 (see also clarity objections under point 1.4). The same applies to the amount of 0.5% w/w of isopropyl myristate, which can be considered as included within the range of "about 0.6% to about 1.2% w/w", as claimed in present claim 1 and to the amount of 4.72% of 0.1 N NaOH, which is regarded as falling within the range of "about 6.5% to about 7.5% (w/w)", as claimed in present independent claim 28.
Therefore, the subject-matter of independent claim 1, 28, 36, 40 and 43 is regarded as not novel under Article 33(1) PCT also over D2, D3 and D4.

3. Inventive Step (Article 33(3) PCT).
Even if novelty could be restored over documents D1 to D4 for the subject-matter of independent claims 1 and 28, the attention of the Applicant is drawn to the fact that the subject-matter said claims might not involve an inventive step in the sense of Article 33(3) PCT.

3.1 Document D3 could be regarded as being the closest prior art to the subject-matter of both independent claims 1 and 28. It discloses a method for treating hypogonadism in a male subject comprising the steps of:
a. providing a hydroalcoholic gel compositions comprising:
- i. testosterone (1% w/w);
- ii. isopropyl myristate (0.705 % w/w);
- iii. ethanol (67% w/w);
- iv. a thickening agent (Carbopol 980, a polymer of acrylic acid) in an amount (0.90% w/w) to give the composition a viscosity of more that 9000 cps;
- v. 0.1N NaOH (4.72% w/w);
- vi. water;

b. administering a therapeutically effective dose of the composition to an area of skin of the subject (see D3, Example 2).
It does not disclose that:
- testosterone is exactly in the range of 1.15% to 1.8% (w/w) or 1.40% to 1.8% (w/w);
- 0.1N NaOH is exactly in the range of 6.5% to 7.5% (w/w).

According to the present application, no particular effect appears to arise from the selection of said range for NaOH. On the other hand, the selection of said range for testosterone, together with the selection of specific amounts of other excipients, appears to bring about an increase of the in vitro permeation of testosterone from the

gel to the skin (see description, paragraphs [069]-[130]).
The problem to be solved by the present invention may therefore be regarded as how to provide improved compositions of testosterone for the treatment of hypogonadism.
Anyway, increasing the amount of testosterone appears to be an obvious solution for increasing its release from the gel. Furthermore, the advantage shown in the present application appears to be due also to the specific excipient compositions, rather than only to the selection of the amount of testosterone.
In particular, in Examples 1 and 4 an improvement in testosterone permeation is shown for formulations F57, F58 and F59, when compared to F56 (marketed product).
Said improvement, anyway, appears to be obvious because formulations F57, F58 and F59 contain a double amount of isopropyl myristate (permeation enhancer) and an higher amount of testosterone than F56.
Therefore, the solution proposed in independent claims 1 and 28 of the present application could not be considered as involving an inventive step (Article 33(3) PCT).

3.2 Dependent claims 2 to 27, 29 to 35, 37 to 39, 41, 42 and 44 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step.
Furthermore, it should be noticed that said dependent claims are only allowable in combination with independent claims meeting the requirements of the PCT in regard to novelty and inventive step.

3. Industrial applicability.

For the assessment of the present claims 1 to 35 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.